Wetherill (H. M.) Jr.

THE MODERN HYPNOTICS.

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The past few years have witnessed the birth of a multitude of new chemical compounds, most of which have well-marked physiological action, and are mainly divisible into three classes—those derivatives of coal-tar whose principal effects are to cause a lowering of the animal temperature and antisepsis; those of the ether series of compounds which have an anæsthetic and hypnotic action when inhaled or otherwise introduced into the system; and a third important and very different group of complex organic composition, which are the so-called active principles of vegetable life. It is with some members of the two latter groups that we will deal in the present inquiry.

The remarkable impetus received by organic chemistry through the activity of the modern, and especially of the German chemists, is responsible for the appearance of a new remedy, frequently an hypnotic, every few months; taxing the attention of the physician to become familiar with even its name and physical properties, to say nothing of the time and application necessary to investigate its individual merits.

The profession of medicine, and especially those of it who daily minister to the requirements of the insane, has been upon the outlook for the ideal hypnotic, but it is unreasonable to hope to find in a single one all the properties requisite to overcome the many and varied causes of insomnia. It is an humiliating admission, (which has truth for its justification) that our present knowledge of therapeutics is largely empirical, and it is thus of necessity that we turn, in an emergency in treatment, to a list of drugs having supposed identical, or closely similar physiological action. This fact must form the chief excuse for the search for and the employment of so great a number of more or less hypnotic substances, and it is a common experience to be disappointed in a given case in the action of a remedy which may have answered a useful purpose in another case as nearly similar in conditions and indications as possible. It should always be the aim of the practitioner to have a scientific motive for every dose prescribed, as it is far safer and more honest to leave Nature to struggle single handed with the malady than to medicate haphazard. The habit

of routine administration of drugs is one into which the asylum physician is especially prone to fall, and it is all the more difficult to avoid, because the temptation to do so is strong, amid the harrassing small details daily recurring in hospital life. It has been recently demonstrated by one of our staff (Dr. E. N. Brush) that there are many instances of insomnia in hospital as well as in private practice which neither require nor should receive strictly medical treatment, but which were relievable by a course of baths, massage and special nourishment in the evening, yet the fact remains that the large majority of the insomnious insane require relief by the administration of sedatives or hypnotics, and the problem confronts us—1st. What is the nature and physiological action of these recently introduced medicines? 2d. What is their relative hypnotic power? 3d. What special indications should guide us in the selection of any one from the others, in prescribing?

In order to attempt the solution of these in an intelligible manner, let us take up, as briefly as possible, the consideration of the most important of these new substances seriatim.

HYOSCYAMINE AND ITS SULPHATE.

This member of the vegetable group cannot be classed as strictly a new remedy, as a substance which he named hyoscyamine was extracted from the fresh seeds of H. niger by Brandes, in 1820; but as it remained for years a mere chemical curiosity, and had since appeared on the market at intervals in such diverse forms and potencies as to lead to general distrust, it may be considered therapeutically new since its revival in a reliable form by the German chemists, led by E. Merck of Darmstadt.

Prior to this the alkaloid was represented in trade by clear, purified resins, and by soft, waxy extractives in which could be found, by the microscope, a few warty crystals, and these preparations varied in activity from utter inertness to the proportionate strength of a recent, well prepared solid extract of the fresh German leaves.

In 1833, Geiger and Hesse succeeded in producing a similar substance having rather more potency, but as little reliability. Kemper in 1866 improved a little upon the efforts of his predecessors, but it was not until 1871 that Höhn succeeded in freeing it, in the form of small, white crystals, from the inert mass of resin, fixed oil and extractives that had held it captive previously.

Thibault, in 1875, crystallized hyoscyamine in a state of purity from a chloroformic solution of mixed resins and waxy, oily by-products. The fresh leaves contain more hyoscyamine than either the roots or the seeds of H. niger. Ladenburg has recently studied carefully the several sources of the alkaloids of the natural order solanaceæ, of which the three important are atropia, hyoscyamine and hyoscine, all of which are represented by the formula C_{17}, H_{23}, NO_3, but differ radically in physical and physiological properties. Of these hyoscyamine is found in atropa belladonna, in datura stramonium, in hyoscyamus niger and in duboisia myoporoides, while hyoscine is found only in hyoscyamus niger. It having been observed that in working upon belladonna root, according to the manner of operating, sometimes more hyoscyamine and sometimes more atropia was obtained, experiments have been made that led to the following conclusions: 1st. That in belladonna root of good quality scarcely any atropia exists already formed, but only hyoscyamine. 2d. That from any belladonna roots, according to the manner of operating, it is possible to obtain, at will, either hyoscyamine, or so-called "heavy atropia," or a mixture of the two.

When oxidized, say by hydrochloric acid, hyoscine splits into tropine and tropic acid, and hyoscyamine similarly treated breaks up into several analagous substances. The pure alkaloid hyoscyamine, as is the case with all such derivatives, is difficult of solution in water, but the chemists present a sulphate of hyoscyamine in two forms: one crystallized in yellowish-white masses and scales; the other in an apparently amorphous form, purely white, in which it resembles small masses of carbonate of magnesium. If this latter be examined under the microscope, it will be found to be minutely crystalline. These two sulphates are in every way identical: the former having been a result of the spontaneous evaporation of a solution, the latter the result of precipitation.

These two salts, as they are at present offered by E. Merck, we have found uniformly reliable, in about equal doses: the so-called amorphous being a little the stronger, grain for grain, as it contained less water of crystallization, and they proved equally and readily soluble in cold water and in alcohol, pure, or variously diluted, forming reasonably permanent solutions. So much for its physical properties.

Our experience in the use of hyoscyamine sulphate dates from the year 1883, and has continued, more or less, to the present time. Series of careful observations were made several times daily upon

groups of selected cases of insanity by the writer, a portion of whose results and tables was published in 1885. The doses ranged from grain 1-60th, which is a proper initial quantity, to grain 1-12th. Two lines of investigation were pursued: one to test the hypnotic power of the drug, the other its supposed sedative action upon conditions of motor excitement in insanity.

Given then at bedtime as an hypnotic, the result showed that in small doses, under grain 1-60th, very little of such action was observed, but that a primary period of excitation and restlessness, followed by a brief stage of muscular relaxation, prevailed in the majority of cases. The continued use of small doses was followed, in a week or ten days, by moderate mydriasis, slight suffusion of the surface, a sense of dryness in the fauces, slight sudorific action, but not sleep.

In larger doses, from grain 1-60th to grain 1-20th, the former the initial dose, a group of fourteen cases of insomnia in female patients suffering from melancholia acute and agitata, mania acute, subacute and chronic and secondary and senile dementia, most of whom were hospital inmates of long standing, in whom a tolerance of and resistance to medication existed, the amorphous hyoscyamine of Merck was administered 268 times, about an equal number of times to each; but one dose in any twenty-four hours, and that usually at bedtime. Careful daily observations were made by the writer, assisted by a few intelligent attendants, and tabulated. This yielded about nineteen administrations to each patient.

A good night's sleep, 6 to 7 hours or more,	resulted in	73	instances.
A fair night's sleep, 4 to 5 "	"	68	"
A poor night's sleep, 2½ to 3½ hours,	"	87	"
A total failure to sleep,	"	40	"
Total, ...		268	

Which is 27.23 per cent of success, and about 15 per cent of failure of any hypnotic effect.

Examined in the morning:

Dryness of the throat and unusual thirst were found	in	189	instances.
Vertigo, "	"	68	"
Muscular relaxation and sense of wretchedness resulted	in	148	"
Transient mydriasis	"	169	"
Pulse quickened and diminished in force	"	199	"
Pulse weak or irregular, or intermittent	"	64	"
Morning appetite impaired	"	96	"

Morning temperature, respiration and condition of skin were not affected. The initial doses were hypodermatic, but the drug was so promptly active when given by the stomach, with equal energy, in the same doses, that the latter mode was preferred, the aqueous solution containing a small proportion of alcohol, to insure its integrity. The foregoing signs and symptoms do not embrace the entire range of physiological effects of the drug, which were best demonstrated in another group of cases, in which the sedative and motor depressant powers of hyoscyamine were tested during daytime. Let it suffice to say of this, that given in full doses, from grain 1-8th to grain 1-10th to active, turbulent cases of mania, acute and chronic, and of secondary dementia, within from fifteen to twenty minutes, the most complete muscular relaxation followed a a brief primary stage of activity, resembling a similar stage of alcoholic intoxication. During the secondary, or period of relaxation, the following phenomena were prominent, from a state of noisy, activity the patient was rather suddenly overcome; staggered about, sank down into a seat, sometimes on the floor, in complete relaxation, with slowed, often stertorous respiration, countenance expressive of misery, widely dilated pupils, marked slowing of the pulse, with increased fulness, suffusion of the face, hebetude and somnolency, and in about one-fifth of the cases, with a slight rise of the axillary temperature. This period would continue for from three to four hours, when the patient would gradually pass into the third or stage of reaction, during which the pulse would be accelerated decreasing in force, until the normal balance, and the previous and usual state of the system as to the other effects was resumed.

At this period a sense of dryness of the throat, hoarseness and unusual thirst was observed in the majority of cases. In a few instances, and not invariably in the same individuals, at the height of the relaxation, Cheyne-Stokes respiration occurred, and the bladder was emptied involuntarily. In most of these cases the appetite was temporarily impaired. The long secondary period of relaxation has caused this drug to be used as a means of so-called "chemical restraint," and but few hospital patients can acquire sufficient resisting powers to withstand its influence for a time at least; but its continued use rapidly breeds a tolerance of its sedative and relaxing effects, demanding a frequent increase of the dose employed.

The writer would here explain that it is not the practice of our hospital staff to use chemical restraint, and that our continuous use of

hyoscyamine and similar sedatives ceased after their physiological action had been investigated, save in those instances when their use was indicated as a special remedial measure.

As an hypnotic, hyoscyamine, in our hands proved to be uncertain and unsatisfactory; very often failing to induce sleep; seldom failing to develop a train of unpleasant phenomena such as before mentioned. It is in no true sense analgesic. The best results from its use in insomnia, were in cases of apparently pure motor excitation. It acts least favorably in atonic mental states and in mere perturbed nervous conditions; its depressing influence upon the circulation being very marked in some such cases. Although it has been highly recommended in the passionate outbreaks and nocturnal turbulence of the epileptic insane, (Dr. T. Brown, *British Medical Journal*, November 25th, 1882,) and in similar states in paretic dementia, (*Richter, Neurologisches Centralblatt*, July, 1882,) yet our experience with females, is against its use in these, as well as in all cases of actual brain lesion or acute structural metamorphosis. Hyoscyamine is often useful in controlling the violence of a furious maniac, but its use, in even moderate doses, demands caution, as its sedative action on the heart is sometimes extreme. A full does causes primarily increased frequency of the action of the heart and vascular tonus; secondarily, in about twenty minutes, a fall below the normal in both, and finally a frequency which is doubtless a reaction toward the normal balance of the circulation. It should be used with much caution in organic and in marked functional and trophic cardiac disorders. The therapeutic value and general scope of applicability of hyoscyamine is far below that of its companion hyoscine, which we will next consider.

HYOSCINE—HYOSCINE HYDROBROMATE AND HYDRIODATE.

This valuable derivative is not chemically of recent origin, having been recognized and separated in an impure state by the same earlier chemists whose investigations produced hyoscyamine. It was originally known as hyoscina, and recognized as distinctly differing in physical properties, in physiological action and in potency from its brother alkaloid. It is significant that, while hyoscyamine is, as before stated, abundantly found in several members of the natural order solanaceæ, hyoscine is only found in Hyoscyamus niger, and, in less amount in other henbanes.

Prior to 1883 no one had succeeded in crystallizing this drug save as a double chloride of gold and hyoscine, its closest form

of concentration uncombined was a syrupy fluid, resembling in appearance the alkaloid conia, from conium maculatum. As a demonstration of the close relationship existing between all the active alkaloids of the order Solanaceæ, it has been recently discovered that the supposed special alkaloid of datura stramonium, separated from it in 1821 by Brandes and by him named daturine is simply a mixture of hyoscyamine and atropia. Another of his supposed crystalline vegetable derivatives finally proved to be phosphate of magnesium! Again, the effect of oxidizing hyoscine by any mineral acid, is the production of tropine and tropic acid: Ladenburg took these two oxidation products, united them and obtained pure atropia.

Prof. Edelfsen, after trying many concluded, as did subsequently the other manipulators that the most stable and reliable combinations of hyoscine were the hydriodate, expressed by the formula C_{17}, H_{23}, NO_5 H. I. $\frac{1}{2}$, H_2, O, and the hydrobromate, C_{17}, H_{23}, NO_5, H. Br, $\frac{1}{2}$, H_2, O, of which the former is only moderately soluble, and occurs in small hemihedral prisms of a yellowish white color; but the hydrobromate is very soluble in water at all temperatures, and in diluted alcohol. It crystallizes in relatively large rhombic, sphenoid, hemihedral prisms, colorless and transparent when first made but soon changing to white opacity from loss of uncombined water.

Unfortunately hyoscine, on its first appearance in the United States was introduced mistakenly as amorphous hyoscyamine with which it was confounded, and thus, for a time much confusion of ideas had existed among those not very familiar with chemicals, which had led to the substitution of hyoscyamine for hyoscine in trade orders, and consequently to the most diverse and contrary experiences as to its potency and precise mode of action. There are various other sources of error which may possibly account for the reports of investigators as to the alleged inertness, impotency and unreliability of hyoscine, one of which is that it deteriorates when long kept or exposed, and thus should be held in stock in small amounts, carefully sealed in glass tubes, in a dark and dry place. The writer has been reliably informed that there appeared in the drug trade of the eastern seaboard at a time of very active, early demand and limited supply of Merck's hyoscine, a fictitious substance, under that trade name and label, which crudely resembled it, but which was almost inert.

During the brief run of this fraud, it must have shaped the adverse opinion of more than one investigator of hyoscine. Some

of this was forwarded, in its original package, for examination, to one of the most experienced importing and manufacturing chemists in this country, who reported that the package contained no hyoscine whatever, and that E. Merck would certainly disown it. Observing proper care, there is no difficulty in obtaining the pure drug, which is a uniformly powerful remedy in doses of grains 1-200th to grains 1-50th. Its sedative powers in insanity with much motor-excitation were tested by the writer, in the same manner as with hyoscyamine, during the daytime, and a portion of the cases tabulated. (See the accompanying tables.) The results showed that in from moderate grain 1-120th, to full doses, grain 1-90th to 1-50th, its physiological action on pulse, respiration, temperature, skin and pupils was about identical with that of hyoscyamine, but to a much less degree, and with much less profound muscular relaxation and sense of wretchedness: much less disturbance of appetite than with the latter, and very much more hypnotic power. In short, the unpleasant effects were mitigated and much sound sleep obtained in daytime, by those whose usual state was turbulent. It was also found that the range of applicability of hyoscine as a sedative extended beyond the cases of more purely motor disturbance, and that in doses of from grain 1-200th to grain 1-90th it could be relied upon to relieve the mental pain in atonic cases, and in those of nervous and so-called hysterical perturbation.

Its action is far more comfortable, uniform and certain than that of hyoscyamine, nor is a tolerance easily established, which would demand frequent increase in the dose. Its beneficial sedative action in the excitement of paretic dementia and of epileptic insanity, is in favorable contrast with the variable and unreliable action of hyoscyamine in the same conditions. The writer, after much observation of the effects of various preparations of hyoscyamus niger, has met with but one instance, in which its use apparently intensified hallucinations of sight or of hearing.

Our experience with hyoscine proved that both in its sedative and its hypnotic action, what effect fails from a full dose, is often realized from one or two small doses. As a hypnotic it was tested in the following tabulated report. (See accompanying tables.) A group of twenty cases of insomnia in females suffering from melancholia, acute, chronic and agitata; mania, acute, sub-acute and chronic; secondary and paretic dementia and of morphia habit, about half of whom were long standing, and tolerant of medicine, was given, chiefly at bedtime, in doses ranging from grain 1-240th

to grain 1-90th, (but as an average grain 1-120th,) the pure, crystalline hydrobromate of hyoscine of E. Merck, in aqueous solution, 348 times. This yielded about seventeen administrations to each patient. The effects were closely watched by the writer, assisted by a few intelligent attendants and night nurses. Of this number

A good night's sleep, six to seven hours or more, resulted in...	246	instances.
A fair night's sleep, four and-one-half to five hours, resulted in	55	"
A poor night's sleep, two and one-half to three and one-half hours, or broken naps, resulted in.....	33	"
A total failure to sleep resulted in.....	14	"
Total.....	348	"

which yields about seventy-one per cent of success and four per cent of failure of any hypnotic effect.

Examined in the morning:

Dryness of throat and unusual thirst were experienced in.....	32	instances.
Vertigo, slight and transient was experienced in.....	19	"
Muscular relaxation (wretchedness) was experienced in.....	14	"
Transient mydriasis was experienced in.....	99	"
Pulse quickened and diminished in force resulted in.....	104	"
Pulse weak, irregular or intermittent resulted in.....	28	"
Morning appetite impaired in.....	29	"

Morning temperature and condition of skin unaffected in any case.

Comparing these gratifying results, which have been fully sustained and corroborated by several years of subsequent daily use, with those obtained from the sulphates of hyoscyamine, we find a good, reliable hypnotic, with little of the unpleasant action of the latter, and a patient will respond to a dose nightly of grain 1-20th for many weeks, obtaining tranquil sleep, without the necessity for an increase in the dose. Dr. E. N. Brush, of our staff, reports much success with it in the insomnia of inebriety and the morphia habit.

It has been, from the time of its introduction, our main reliance in certain cases, and it is but just to testify that the condition of our disturbed wards has totally changed for the better, in great part owing to its judicious administration. An inspection of our records and night reports yield abundant testimony to the quieter nights and vastly improved sleep of those under our care since its use.

Hyoscine totally fails sometimes, as do all medicines, and it is much easier to ask than to answer the pertinent question, under what circumstances does it fail, or when is its use contraindicated? The writer has been watching its action daily for several years,

and can only answer that its use is contraindicated in advanced cardiac lesion, in grave cardiac weakness, and in states of profound exhaustion. In mental disorders its range of general applicability seems to be almost universal, but with occasional failure, for which it is difficult to account. Individual idiosyncrasy is a term used as a shield to our ignorance of its effect on certain constitutions, or under certain circumstances.

The good effects of hyoscine are as evident in atonic, sluggish forms of mental disorder, as in the sthenic, and its power to calm the violence of paretic and epileptic dementia is only equaled by the relief it affords to the insomnia of alcoholism and of the morphia habit. It acts promptly, usually within thirty minutes, and almost as rapidly, and quite as effectively by the mouth as hypodermatically. The smallness of the dose, its tastelessness, and the ease with which it may be given in food and in drink, further commend it, as does also the improbability of inducing a hyoscine habit, as no sense of pleasurable stimulation belongs to its physiological action, such as distinguishes that of so many remedies, among which is paraldehyde, which we will next consider.

PARALDEHYDE.

This is a member of the ether series, is at ordinary temperatures fluid, but crystallizes into an ice-like mass at the comparatively high temperature of 10° C., and thaws unchanged, and is transparent, light, colorless: boils at 134°C. (253.7°F.) and has a rather unpleasant, ethereal odor, resembling that of aldehyde, and an unpleasant burning taste, which renders it difficult to swallow even when diluted. Paraldehyde is the condensation product of aldehyde and hydrochloric acid. It is formed by adding to the former a small amount of the latter, when the condensation takes place with evolution of heat. The product is cooled by ice till it solidifies, is then pressed to free it from acid, &c., and is finally distilled. Distillation with sulphuric acid reconverts it into ordinary aldehyde. Aldehyde, its related compound, is as the name implies, dehydrogenated alcohol, and is represented by the formula C_2, H_4, O; paraldehyde is simply a modified form of the same, of the formula 3 (C_2, H_4, O), but closely related as they are chemically they differ strikingly in their action upon the animal economy.

Paraldehyde was introduced a few years ago from Germany as an hypnotic of peculiar merit, since when its demand has steadily increased, notwithstanding the difficulty in exhibiting

even in moderate doses in a palatable form. Its hypnotic dose is from two to six grammes, and two grammes of it measures just thirty minims—a moderate commencing dose, and twice this a fluid drachm, is a fair medium dose—six grammes, or ℥ iss a full one. It is least unpleasant to take in the following way: ℞: paraldehyde ℥ i; Jamaica rum ℥ iv, syrup of acacia ℥ iii slightly diluted with water; or, ℞: paraldehyde ℥ i, syrup of tolu: ℥ iii, cinnamon water ℥ iv.

Of Merck's paraldehyde one fluid drachm will remain dissolved in nine fluid drachms of cold water; but this is almost as difficult to swallow as the drug itself. The burning, acrid, choking sensation, which is persistent, renders its administration, especially to the insane, difficult. In asylum practice it is often convenient, but not always desirable, to give it in whisky, which also fairly disguises the taste.

It has been stated that this substance loses its power; changes radically, if exposed to the atmosphere for even a brief time. This is a fallacy: it is volatile, and loses on exposure, but what remains is chemically paraldehyde, to the last drop. Much has been written upon this new remedy, based upon scientific research, here and abroad. Profs. Arpad Bockai and Barksi of Klausenburg, in a series of observations upon dogs, gave large, but not fatal doses of paraldehyde to one group, and similar doses of chloral hydrate to another, for long periods. "The organism did not become tolerant of either drug, but its power of resistance rather became less, the latter condition being more marked with paraldehyde than chloral." From this they concluded "that during long continued use, the dose of these drugs need not be increased. The animals perished from the chloral in about half the time as from paraldehyde." This only proves that these doses need not be increased when giving these remedies to dogs, as in man a tolerance of and resistance to chloral is of common experience, and the same may be said, but less frequently, of paraldehyde. They finally concluded "that paraldehyde, given for a long time, effects incomparably less injury, than the long continued use of chloral hydrate." A more significant indication of its mode of action is revealed in the observations of Drs. Bergesio and Mosso (*London Medical Record*, Oct. 15, 1884), who "having a patient who had lost a large portion of the calvarium, they were enabled to make a study of the cerebral circulation, which confirmed the view that the brain is anæmic during sleep. Paraldehyde gave the same result as natural sleep. Morphia and alcohol

notably increased endo-cranial congestion: that the hypnotic effect of these two latter drugs does not depend on change in the blood pressure, but upon some special action, possibly of a chemical nature, upon the cerebral cortex." We can confirm the statement that paraldehyde does slowly diminish the force and frequency of the heart's action.

Dr. Clouston says (in *American Journal of Medical Science*, April, 1889), "this pure hypnotic, after extensively employing it, I like better than any I have tried. * * * * It does not interfere with the appetite, nor does it disturb the stomach or bowels. After a paraldehyde sleep there is no lassitude; no headache." Dr. G. F. Duffy concludes from a long continued series of experiments that "it acts first on the cerebral hemispheres and causes torpor without preliminary excitement. After the hemispheres the action extends to the medulla, then to the cord. A lethal dose suspends the function of the medulla and the respiratory centre, and the action of the heart ceases after the respiration."

It seems to be an established fact that in common with urethane, this drug is antagonistic to the action of strychnia, even in poisonous doses. For several years past the writer has steadily used and carefully studied the effects of paraldehyde in our hospital, and has been encouraged to continue on account of its purely hypnotic action in the insomnia of certain forms of insanity, in the average dose of one fluid drachm; disguised with syrup tolu, and one of the aromatic waters. This has proved the most suitable method as, when alcohol, in any form, or spirits chloroform or other active substance is used as an excipient, as has been often recommended, we introduce an unknown quantity into the problem of its effect upon the organism, and then who is to say whether drug or excipient induced the repose, or to what extent its action was modified thereby? In our hands it has acted best in cases of melancholia in its various forms; in cases with a strong hysterical element; in those beset with delusions of fear, of doubt, or of dread of impending calamity; in the agitated who pace the floor at night, wringing their hands, and in the demented who are ordinarily quiet in daytime but are disturbed at night. Much less success has attended its use in mania of all forms, either in moderate doses repeated at short intervals, or in a single full dose at bedtime; the latter answering better than the former, as, in excited states there is a primary excitation often produced which is repeated and intensified by subsequent doses. In the conditions previously cited in which the drug acted most favorably, this

primary excitation was seldom observed; the patient sinking to sleep usually within thirty minutes after its ingestion, obtaining from five to seven hours of tranquil repose, and awaking refreshed, without unpleasant after-effects. This in the majority of such cases, but not always so; for in twenty cases there were two (of melancholia agitata) in whom the respiration was weakened and hurried, with a sense of cardiac oppression, after any dose. In several other instances, in different cases, after an evening dose of ʒ i, followed by sleep, were experienced headache (frontal) nausea, coated tongue, and increased mental depression, which yielded upon the withdrawal of the medicine, and returned upon its subsequent use. It sometimes caused similar sensations in instances when sleep failed to follow its use at bedtime. In about half of the cases observed, which was twenty-six in all, was the amount of urine apparently moderately increased by its continued use, the urine being paler and more watery, but quite free from ethereal odor. Its elimination takes place mainly through the lungs, but, in part also, evidently by the skin; the sweat and the expired breath of those taking it nightly, being seldom free from the characteristic odor. When pain is an element in insomnia paraldehyde fails to overcome it. We have observed, in a few cases of epileptic insanity, in whom the paroxysms were chiefly nocturnal, much improved sleep, and marked diminution in the number and severity of the paroxysms, by a bedtime dose of one fluid drachm. Paraldehyde was tested by the writer in a group of twenty-six insomnious hospital cases as follows: The drug was given 424 times, about an equal numer of times to each. There were of mania, acute 3, subacute 3, chronic 4, melancholia acute 2, agitata 2, subacute 3, chronic 3, dementia senile 1, secondary 3 and epileptic 2 cases—26 in all.

The doses ranged from ʒ i to ʒ ii; but the former in the majority of cases, and but one dose was given to each patient at bedtime; all other drugs being withheld.

Complete success, from six to eight hours or more of continuous sleep, resulted in	291 instances.
Fair success, from four-and-one-half to five hours or more of continuous sleep, resulted in	22 instances.
Partial failure, from three to four hours or broken naps, resulted in	42 instances.
Total failure to sleep resulted in	69 instances.
This yields of complete success about 68.7 per cent, and of total failure of hypnotic power	16¼ per cent.

Paraldehyde is a fairly reliable hypnotic, chiefly in the asthenic forms of mental disorder, and, but for its unpleasant taste and lingering effect upon the expired breath, could be used in the asylum practice much more freely than it now is. No case of death from its legitimate use has, as yet been reported, although it has been and may safely be used in the insomnia of cardiac affections, with less risk than any other allied compound save sulphonal. A few cases have been reported in which the paraldehyde habit has been contracted; but using due professional caution, the danger of so doing would be trifling.

The sleep produced by this drug has often been compared to that by chloral hydrate; but the consensus of opinion among those who have investigated both substances is that paraldehyde is the much safer of the two to employ continuously, as in nervous insomnia and in that of drunkards it is much superior to chloral; less irritating to and better born by the stomach; it is not a cardiac depressant, nor does there usually exist the necessity for rapidly augmenting the dose, as is so frequently the case in the steady use of chloral hydrate.

URETHANE.

This is another member of the ethereal group of hypnotics, and is chemically the carbamidate of ethyl, of the formula (NH_2, CO_2, C_2H_5). It is a solid, in large, irregular plates and crystals, opaque white in color, without odor, and of a taste at first slightly sweet, afterward faintly bitter: is readily soluble in water at all temperatures, forming a permanent solution. This recent addition to the hypnotics comes to us from Germany. Its advent was, as usual, heralded by such glowing accounts of its powers, as might have aroused the hope that the ideal hypnotic was upon us; but calm experience has failed to verify its superiority over paraldehyde. Merck's pure urethane is the one principally, if not universally used in this country, and appears to be pure and uniform in its action and physical properties. From experiments by Prof. Coze with it in the lower animals, it would appear that, in a large dog, the effect of strichnia grain 1-5th was thoroughly counteracted by grains 75 of urethane, and that the animal survived both doses; it further appeared that the amount of oxygen in the blood is notably increased by its presence, which may possibly account for the frequent failure of urethane to produce sleep. Unlike paraldehyde and sulphonal, it appears to be moderately analgesic, and some relief has resulted from its use in the restlessness from pain

in gout and in rheumatism. The Italian asylum physicians, after a very thorough trial, report a rather unfavorable experience with it. Dr. Sighicelli, of the Ferrara hospital, says: "Urethan proved uncertain in all forms of insanity, as an hypnotic, even in melancholia and dementia. Respiration was shallower and slower: on the other hand the heart acted more powerfully and quickly." Drs. Otto and Kœnig (*Centralblatt für Nerven Heilkunde*), after extensive trial among the insane, also report generally unfavorably upon it; but as having most hypnotic effect in cases of paralysis and of dementia without excitement, but with restlessness and nocturnal vigilance; but then in doses of from 5 to 12 grammes, or 75 to 180 grains, which is much in excess of the average dose. Krapelin and Rothenbiller had fair success with it in similar quiet cases, but ill success in disturbed conditions; the former observer having never seen any unpleasant after effects, 60 per cent of his paralytic dements obtaining from six to eight hours of continuous sleep, within fifteen minutes after having taken from 1 to 3 grammes of urethan.

Dr. H. Williams, (*Jour. Amer. Med. Assoc.* Jan. 22, 1887,) of the medical staff of the Arkansas State Asylum, reports a most favorable hypnotic effect from urethane in cases of mania, with much excitement, in the moderate dose of grains 15. He says: "I have found sound, natural sleep to result uniformly after this dose." In our hospital practice we have not been so fortunate, after a fair trial of it, in various doses, and in the various phases of mental disorder. Given in the published dose of 15 grains, it had but little hypnotic effect in cases of mania in any stage, or in any disturbed conditions, while in doses of from 30 to 35 grains there was little more sleep, with considerable morning discomfort, of which the chief elements were nausea, loss of appetite, and persistent frontal headache. In about one-fifth of the cases of a quieter character, such as melancholia, dementia, &c., the drug acted fairly as an hypnotic, but very irregularly, in doses of from 15 to 20 grains. More than these amounts frequently produced impairment of appetite and headache. A full night's sleep, from seven to eight hours, having been rather exceptional, in any condition, under its influence. Repeated subsequent trials with different lots of the drug, have not proved any more satisfactory in our hands, and when, therefore, very recently, a new solid ethereal substance was announced by the chemists of Germany, as the coming hypnotic, we were prepared to look upon it askance.

This compound, sulphonal, deserves, however, more than a passing notice.

SULPHONAL.

In the treatment of insomnia from whatever cause demanding medicine, we aim to use a remedy of which sleep is the sole, or at least the predominant physiological action. It was originally claimed by the manufacturers of sulphonal in Germany, that its sole effect was to cause sleep of a quality very similar to that of nature, and of the many investigators of it, both here and abroad, there has not been one to report unfavorably of its action. The very general consensus of opinion in its favor is all the more singular from the fact that of all the others discussed here different examiners have had the most diverse and puzzling experiences in their use. The almost universal report of sulphonal is that it has little or no effect upon the vast majority of insomnious subjects, save the important one of increasing, prolonging the natural tendency to sleep; that its action is not narcotic, but purely hypnotic; that the pulse, pupils, temperature, respiration, appetite and the secretions remain practically unaffected after its daily use for indefinite periods, and that it is finally promptly eliminated from the system, principally by the kidneys, without irritation or detriment to those organs. Sulphonal is also a member of the ether series, and is a crystalline, white, solid, with a slight tendency to effloresce when exposed to the air, and is easily powdered, emitting, when warmly triturated, a faint odor of sulphur, and it is almost tasteless. It is singularly insoluble in any of the potable solvents, as water, dilute acids or alkalies, or very dilute alcoholic solutions. It is soluble in two parts of ethylic alcohol (95 per ct.) and one of ether, but this is not potable, and any dilution of this with water precipitates the sulphonal. It may be given in powder, or a dose of the finely powdered drug may be suspended in three or four fluid drachms of cold water by means of gum acaciæ and syrup, which should be thoroughly shaken before using, and but one dose prepared at a time, as it rapidly settles to the bottom of the container. It may be conveniently given also, in hot gruel, or in milk.

The name sulphonal is evolved from the compound word which expresses its chemical identity—diæthyl-sulphon-dimethyl-methan, and the actual solubility is one part of the drug to about 100 parts of cold, and one to about 18 or 20 of boiling water, which, of course, drops it on cooling. It is unaffected by acids, alkalies or oxidizing agents: a very stable compound, of the symbol $(CH_3)_2C(C_2H_5SO_2)_2$, and was discovered and named by Prof. Baumann, who, with Prof. Kast, of Freiburg, tested, first on dogs,

afterward on normal human beings, finally upon insomnious persons insane and otherwise ill, its physiological effect in a series of clinical observations, which showed that in doses of 2 to 3 grammes (grains 30 to 45) to persons in health, it produced lassitude, hebetude and sleep; in the same doses to those suffering from nervous and febrile insomnia it caused a sound, refreshing sleep of from five to six hours' duration, within from one-half to two hours after administration. Subsequently Prof. Cramer and Doctor Rabbas obtained similar results upon insane patients in the Marburger Irrenheilanstalt. In no instance did it effect unpleasantly or dangerously; produced no evil effect afterward upon the circulation, respiration, appetite, digestion, secretions nor excretions. The pupils remained unaffected. "Although somewhat slower in taking effect than chloral hydrate (Notes on New Remedies for June, 1888) the action of sulphonal is more prolonged. Doses of 2 to 3 grammes proved safer and more effective than proportionally larger doses of amylen hydrate. Another peculiar and valuable attribute of sulphonal is that its prolonged use does not weaken its physiological effect, nor does it produce the desire for a narcotic, that makes the use of chloral (and some other drugs) so dangerous. Additional and general investigation will doubtless verify the above observations and insure the popularity of this new hypnotic."

The papers by Prof. Kast and Dr. Rabbas were published in 1888 (in the *Berliner Klin. Wochen.*, Nos. 16 and 17.) The latter considers it more desirable than paraldehyde or amylene, and as compared with chloral hydrate, sulphonal is less prompt but more lasting in hypnotic effect. Further corroborative evidence will be found in papers by Langgard u Rabow, (*Ther. Monattshefte*, for May, 1888); by Salgo, (*Wiener Med. Wochen*, No. 20); by Rosin, (in *Berlin. Klin. Wochen*, No. 18); by Astreicher, (in the same); by Cramer, (*Münch. Med. Wochen*, June 12, 1888, p. 395); by Schwalbe, (*Deutsch. Med. Wochen*, June 21, 1888, p. 499); and by Rosenbach, (*Berlin. Klin. Wochen*, June 11, 1888, p. 481.) Astreicher found it best to give the dose several hours before bedtime, as it was rather slower to act than some others of the same class; but he found it none the less reliable, especially in the insomnious insane. Cramer's cases were all of the latter class, and in his 407 trials on 92 insane subjects he had positive success "in 92.6 per cent, *i. e.* from five to nine hours of unbroken sleep, resulting in about half an hour after its administration. He had not an instance of unpleasant effect, "though in one case grains

480 in six days, and in two others grains 45 daily were given for two months." Schwalbe's results are of especial value and reliability, as they were exhaustive and carefully tabulated. He selected fifty patients ill of various bodily and of mental diseases and disorders, all insomnious, and got "a prompt and satisfactory hypnotic effect in 66 per cent." But what is of especial value is the fact that "of twenty-four cases of purely nervous insomnia, success was complete in 90.3 per cent.

To such cases it seems best adapted, for in instances where the sleeplessness was the direct result of pain, or of decided irritation, but 44.4 per cent slept at all, and these but for a few hours. Schwalbe agrees with Kast that the drug is purely hypnotic, not narcotic. It seems decidedly most valuable in perturbed nervous and unbalanced cerebral cases, but in no sense is it analgesic, nor does it allay the nocturnal cough of phthisis, or bronchitis. Contrary to the experience of Kast, Schwalbe found that it did not relieve cardiac dyspnœa.

In but 12 per cent of all cases so far investigated in Europe, were there any ill-effects from its daily use, and this was confined to slight headache or to transient vertigo.

Schwalbe's experience of it in children was satisfactory in doses of four grains: in male adults in doses of from grains 15 to 30, and in female in less doses from grains 12 to 25.

In the department for females of the Pennsylvania Hospital for the Insane, the writer has observed carefully the action of sulphonal upon a group of twenty cases of mental disorder, all of whom had been quite insomnious, so as to resist the sedative force of the bromides with ergot, urethane, tinct. hyoscyamus, English. Eight of them resisted all these and also paraldehyde, seven of them resisted all these as well as opium and chloral hydrate in the usual doses, while all but one of them were usually controlled, *i. e.* slept, by the use of hyoscine hydrobromate, in doses ranging from grain 1-120th to 1-90th. The group comprised three cases of acute melancholia with delusions of fear of bodily harm and of impending calamity; one of dementia, senile; one of melancholia agitata; two of epileptic insanity; two of melancholia, chronic; three of mania acute; two of mania sub-acute; one of mania chronic; four of secondary dementia; and one case of nervous disorder with threatened insanity. Of these all the subacute and the chronic were much accustomed to the effects of sedatives, hypnotics, &c., all requiring night medicine regularly. But one moderate dose of sulphonal, suspended by acaciæ and syrup in water, was given each

patient about an hour before bedtime, and in no instance was the dose repeated, nor were any of them taking any other drug. The group was intelligently observed at night by nurses sitting up. The results were carefully observed and tabulated. The drug was given 480 times, no patient receiving in all less than twenty-one doses. In thirteen of the cases the nightly dose was 15 grains; in four it was 20 grains; in one it was 21 grains; and in one case it was 22 grains.

The results were as follows:

An excellent effect, *i. e.* 6½ to 9 hours of continuous sleep, in				381	instances.
A fairly good	"	4 to 5	" "	34	"
An imperfect	"	2 to 3	" (or broken naps)	42	"
No hypnotic effect				23	"
Total,				480	

This yields of positive successes 79.2 per cent of the entire number, and of total failure of hypnotic action 4¾ per cent.

It is gratifying to note the general improvement which attends the regular nightly sleep produced by such a singularly harmless drug as sulphonal appears to be. In but seven instances had its use for many continuous nights been followed by unpleasant effects, and these were limited to transient morning headache and slight vertigo in two of the patients taking the larger doses. As a rule, with very few exceptions, the patient rises with the usual appetite; free from a sense of malaise. In no instance did it produce any appreciable effect upon the temperature, pulse, respiration, skin, kidneys nor pupils, nor did the digestion appear to be at all impaired by its regular use. The sole physiological action appeared to be the production of sleep, usually quite restful and prolonged.

As the results were good in these hospital cases, tolerant of such drugs, would not probably less doses overcome the insomnia of the simply weary, over-worked or irritable nervous system? It should prove useful in the insomnia of general disease of which pain is not a prominent factor. It will not ease pain, nor will it bring sleep when pain is present as a continuous sensation, but it will allay nervous restlessness, vigilance and agitation. In cases of acute mania, with much motor activity, it does not act nearly so promptly nor effectually as hyoscine, in any doses. Male adults usually require a larger dose by from three to five grains than do females. In the latter a fair average dose is from 15 to 18 grains, but there need be no fear in increasing the amount to 30 or 35

grains. Should no hypnotic effect follow the latter quantity the remedy will fail in any amount.

RECAPITULATION OF RESULTS—HYPNOTIC ACTION.

Hyoscine—positive success, about	71	per cent.
" —total failure,	4	"
Sulphonal—positive success,	79.2	"
" —total failure,	4¾	"
Paraldehyde—positive success,	68.7	"
" —total failure,	16¼	"
Hyoscyamine—positive success,	27.23	"
" —total failure, about	15	"
Urethane—positive success about	13	"
" —total failures,	numerous.	

In concluding this paper the writer would pass by with a brief notice such more or less hypnotic substances of more recent introduction, or of revival, as hypnone, amylen-hydrate, amylen-phenate, ethyl-bromide, ormosine (from the ormosia dasycarpa) Jamaica dogwood, spartein, kava-kava, methylal, because, with scarcely an exception, they have failed to stand the test of applicability to the treatment of insomnia in the insane. Those of the ether series, as hypnone, ethyl-bromide and the amylen compounds are either violent, variable and uncertain in their action and are undesirable from their unpleasant taste, or they disagree with the stomach, impair digestion, and cause unfavorable secondary disturbances. Methylal is said by Krafft-Ebing to be the best remedy that he has tried for paroxysms of delirium tremens. The various amyls and methyls have received, from time to time, favorable notice from contributors to current medical literature, but the mere fact of their remaining in the background of our therapeutical array, is significant of the retirement to which they will be relegated in the near future. The present paper seems to the writer, after much careful trial, and long-continued study of effects, to embrace the most reliable, least variable and least harmful of the more recently introduced hypnotics applicable to the treatment of some forms of insomnia in the insane. If it will be found that in doing so any light has been shed upon the subject of the action of these modern hypnotics, he shall feel fully recompensed for the continuous efforts put forth for several years, and proceed encouraged toward further investigation.*

*Read at the annual meeting of the Association of Medical Superintendents of American Institutions for the Insane, held at Newport, R. I., June 18-20, 1889.